

## Neural circuits of eating behaviour: opportunities for therapeutic development

Article (Accepted Version)

Clifton, Peter G (2017) Neural circuits of eating behaviour: opportunities for therapeutic development. *Journal of Psychopharmacology*, 31 (11). pp. 1388-1402. ISSN 0269-8811

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/74676/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

### **Copyright and reuse:**

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

**Neural Circuits of Eating Behaviour:  
Opportunities for Therapeutic Development**

P. G. Clifton

School of Psychology

University of Sussex

Brighton BN1 9QH

UK

Email: [pete@sussex.ac.uk](mailto:pete@sussex.ac.uk)

## **Abstract**

Understanding of the neural and physiological substrates of hunger and satiety has increased rapidly over the last three decades and has already identified pharmacological targets for the treatment of obesity that have moved from pre-clinical screening to therapies approved by regulatory authorities. This review initially describes the way in which physiological signals of energy availability interact with hedonic and rewarding properties of food to modulate the neural circuitry that supports eating behaviour. This is followed by a brief account of current and promising targets for drug development and a review of the wide range of preclinical paradigms that model important influences on human eating behaviour, and can be used to guide early stages of the drug development process

## Introduction

It is widely acknowledged that the process of taking a novel scientific finding that identifies a potential therapeutic drug target through successful development and introduction of a treatment is fraught with difficulty (Scannell and Bosley, 2016). The reasons include unexpected toxicity and other side effects, as well as a lack of efficacy that becomes apparent as a drug moves from preclinical to clinical stages of testing (Smietana et al., 2016). The development of drugs to treat behavioural and CNS disorders has been particularly prone to these issues (Pangalos et al., 2007).

However there have also been successes, including the early development of dopaminergic therapies, such as L-DOPA and the dopamine receptor agonists pramipexole and ropinirole, for Parkinson's disease (Oertel and Schulz, 2016). In other areas, such as anxiety and depression, drugs have often been identified serendipitously and progress in developing novel and more effective therapies has been slow. However with the recent introduction of several new drug classes, the area of appetite, eating disorders and obesity is one in which new scientific knowledge is capable of driving successful drug discovery programmes.

Changes in body weight are an inevitable consequence of an imbalance between energy input and energy loss, and the first Law of Thermodynamics. However the two sides of this equation are not equivalent to food intake and voluntary activity and the presumption that obesity results from some combination of 'gluttony' or 'sloth' (Prentice and Jebb, 1995) is not justified. Energy in food only become available after complex processes of digestion, which themselves require energy, and it's efficiency is also influenced by variation in the gut microbiome (Ridaura et al., 2013). Energy loss consists of several components apart from voluntary activity, each of which is subject to physiological variation (Blundell, Gibbons, et al., 2015)

In humans daily the 'recommended' daily intake for adult males is about  $10^4$  kJ implying that total energy intake over a span of 50 years will approach  $2 \times 10^8$  kJ. Moreover experiments in which human diets are covertly manipulated have shown that

excess energy intake of about  $3 \times 10^3$  kJ may be associated with the gain of 100g adipose tissue (Prentice and Jebb, 2003). This suggests that even small variation in cumulative energy balance over time has the potential to lead to clinically significant changes in body weight and supports the view that, at some level, energy balance is achieved through the action of a regulated, homeostatic system. However the ability to measure small, but clinically significant, changes in either energy input or output that lead to obesity in 'free-living' humans is quite limited. In addition human energy intake is highly variable on a day to day basis and energy expenditure may also vary as a consequence of under- or over-feeding (Chow and Hall, 2014; Hall, 2010). The physiological and behavioural mechanisms that underlie this linkage of energy intake and expenditure are poorly understood although they may be highly relevant to advancing novel therapies for obesity.

Although energy balance is subject to strong physiological regulation, it has become increasingly clear that feeding behaviour is also strongly influenced by non-homeostatic signals that may derive from a variety of sources. These include broad environmental features such as food availability and palatability (Berthoud, 2012). Prior experience and learning may result in environmental cues associated with palatable or rewarding foods exerting a facilitating effect on intake that overrides or resets homeostatic controls (Weingarten and Martin, 1989). Challenges during foetal and early life may also lead to long lasting effects on feeding and body weight, acting through epigenetic mechanisms (Benite-Ribeiro et al., 2016). 'Acceptable' body size may be set by social and cultural influences. More recently it has also become clear that energy utilisation and expenditure may also be subject to greater variation than previously appreciated (Blundell, Finlayson, et al., 2015).

The probability of the successful development of a novel drug therapy for obesity will be increased if the pharmacological target has been chosen from a knowledge of the neural mechanisms that underlie eating behaviour and has been validated in a range of carefully chosen preclinical models. The following sections of this review discuss each of these areas.

## **Physiological and neural substrates for hunger and satiety**

Hunger, satiation and satiety, are best considered as behavioural constructs that describe changes in the probability of feeding over time. A state of hunger in a non-feeding animal increases the probability that feeding will be initiated, or in the case of an animal that is already feeding, that it will continue to eat. Satiation is the process that leads to the cessation of food intake and satiety is the state in which, as a result of prior ingestion, the initiation of a further bout of food intake is unlikely (Clifton, 2000).

Though it might be argued that satiety and hunger are simply the inverse of one another and that the additional terminology is unnecessary, there are good theoretical reasons why this position can be rejected. In most animals, and particularly in humans, active feeding occupies a small part of the overall time budget. It therefore follows that body energy reserves will increase rapidly during a meal and decrease more slowly between meals. As a consequence, many of the physiological signals of energy balance will lag ingestion. Thus, the termination of a meal is likely to be signalled by early correlates of ingestion whereas meal initiation may be more dependent on more slowly changing signals of energy balance.

### *Gut hormones and their receptors*

The gut is a rich source of both neural and hormonal signals of energy availability that also play an important role in controlling gut motility and the secretion of digestive enzymes and insulin (Gribble and Reimann, 2016). Fasting and satiety are characterised by distinct hormonal profiles. During fasting the raised level of ghrelin, acting via a splice variant of the growth hormone secretagogue receptor (GSHR1a) that is expressed both peripherally and within the CNS, is especially significant in enhancing the motivation to feed. Peripheral locations of this receptor include the beta cells of the pancreas where receptor activation leads to the inhibition of insulin release. The receptor has a broad CNS expression pattern including hypothalamus, hippocampus and several reward-related areas including the ventral striatum (Perelló et al., 2012).

The passage of food down the digestive tract is associated with the release of gastrin and somatostatin (SST) from the stomach, and gastro-intestinal peptide (GIP), cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), oxyntomodulin, and peptide-YY (PYY) as partially digested food moves to the small intestine (Gribble and Reimann, 2016). Receptors for each of these hormones are expressed peripherally and in the brain, and their endogenous ligands may also be locally synthesised within the CNS. CCK-1 receptors are expressed in afferent vagal fibres and several hindbrain and hypothalamic nuclei whereas the CCK-2 receptors have a much more widespread CNS distribution (Moran and Kinzig, 2004). GLP-1 containing cell bodies are restricted to a group of non-catecholaminergic cells in the caudal nucleus of the solitary tract (Larsen et al., 1997). However GLP-1 receptors are widely distributed in the CNS in areas including hypothalamus, ventral tegmental area and a number of brainstem sites relevant to feeding behaviour (Göke et al., 1995). PYY receptors have a similarly widespread CNS distribution (Karra et al., 2009) and there is a restricted group of PYY-expressing cells in the gigantocellular reticular nucleus of the rostral medulla (Gelegen et al., 2012). It is likely that some of these receptor populations will also be able to sense circulating PYY. Oxyntomodulin reduces gastric acid secretion and is an agonist at glucagon and GLP-1 receptors.

In addition to gut-derived peptides there are several other hormonal systems that may exert powerful effects on appetite. These include the adipokine leptin, the pancreatic hormones insulin and glucagon and adrenal corticosteroids. The CNS distribution of leptin receptors in the brainstem and hypothalamus is similar to that for ghrelin, although co-expression of these two receptors in individual neurons is rare (Perelló et al., 2012). Insulin receptors are also widely expressed in the CNS, both in structures classically associated with feeding behaviour, such as the hypothalamus, as well as in other areas such as piriform cortex, hippocampus and choroid plexus (Blázquez et al., 2014).

*Brain structures implicated in the control of feeding behaviour*

Given the relatively widespread CNS distribution of receptors for gut-derived hormones, the CNS circuits that modulate feeding behaviour might similarly be broadly distributed, although it would also be consistent with them having functions independent from the modulation of feeding behaviour in some cases. Seminal studies of hypothalamic function suggested a dual centre hypothesis for the hypothalamic control of appetite (Anand and Brobeck, 1951; Hetherington and Ranson, 1942) that dominated the field until at least the late 1980's, but evidence has now accumulated to support the concept of a broader distributed CNS system in feeding behaviour (Kelley et al., 2005). The components of this system, aside from the hypothalamus, include specific brainstem nuclei, including the nucleus of the solitary tract (NTS) and lateral parabrachial nucleus (PBN), reward-related areas such as ventral tegmental area and ventral striatum and specific cortical areas, such as orbitofrontal cortex.

*Brainstem.* Several brainstem nuclei (Figure 1A) play an important role in feeding (Grill and Hayes, 2012). The NTS has a key role in the integration of interoceptive inputs and modulation of forebrain systems that both mediate homeostatic and reward-related functions (DL Williams, 2014). It receives vagal inputs from the gut that signal stretch and tension resulting from ingestion of food, in part mediated by 5-HT<sub>3</sub> receptors. Cells of the NTS also express receptors for leptin, ghrelin and other gut peptides, and receive vagal inputs from cells in the nodose ganglion of the vagus nerve that also express receptors for this group of peptides (Grill and Hayes, 2012). It is likely that stimulation of vagal CCK-1 receptors is important in the short term satiety-enhancing action of CCK (Moran and Kinzig, 2004). CCK-expressing neurons are also present in the NTS and activation of these cells has complex, pathway-specific effects. Activation of the cell bodies using a Cre-dependent Gq-coupled DREADD receptor activated by clozapine-N-oxide (CNO) resulted in an aversive effect (Roman et al., 2017). In the same study it was shown that optogenetic stimulation of the projection of these cells to the parabrachial nucleus (PBN) had a similar aversive effect whereas similar stimulation of the projection to the paraventricular hypothalamus (PVH) had an appetitive component when measured by a real time place preference task (Roman et



al., 2017). In this context it is important to note that the behavioural satiety sequence obtained after systemic administration of CCK resembles that of true satiety rather than an aversive state (Halford et al., 1998). Leptin signalling in the NTS can serve to amplify the effects of vagal GI signals on eating by directly influencing meal size (Kanoski et al., 2012). In addition the NTS and other hindbrain nuclei may be directly sensitive to circulating glucose levels (Jordan et al., 2010). The NTS contains a small number of GLP-1-containing cells that project to the hypothalamus, including the arcuate, paraventricular and lateral nuclei, and also to the core and shell of the nucleus accumbens (Williams, 2014). This circuitry demonstrates the way in which NTS may, by sensing neuronal and hormonal signals associated with eating, influence both homeostatic and reward-related functions. The NTS also receives forebrain inputs that may serve to modulate eating behaviour. For example, orexin-containing neurons in the lateral nucleus of the hypothalamus project to NTS, and 4<sup>th</sup> ventricle administration of the orexin antagonist SB334867 reduces meal size (Parise et al., 2011). Proopiomelanocortin (POMC) expressing cells in the NTS are activated by CCK and the hypophagic effect of CCK requires activation of central MC-4 receptors (Fan et al., 2004).

The area postrema (AP), just dorsal to the NTS, is a circumventricular organ with a limited blood-brain barrier. Cells in this area have receptors for leptin and are also sensitive to blood born toxins, contributing to the development of conditioned taste aversions. The AP is an important site of action for the effects of the pancreatic hormone amylin, which is co-secreted with insulin and can have a strong inhibitory influence on eating behaviour (Lutz, 2013). Infusion of an amylin antagonist into AP increases food intake (Mollet et al., 2004) and systemic administration of the amylin agonist salmon calcitonin, which has an extended duration of action, reduces phasic dopamine release in the nucleus accumbens, an effect abolished by lesions of either AP or the parabrachial nucleus (PBN) (Whiting et al., 2017). Calcitonin-like gene related protein-expressing cells projecting from AP to the ventral tegmental area (VTA) may mediate this effect. Amylin can also enhance the effects of leptin, CCK and GLP-1

on eating through interactions in both AP and in forebrain areas. There is a substantial mixed noradrenergic and serotonergic projection from AP to the PBN, which may act as the onward signalling pathway for these actions of amylin (Miceli et al., 1987). The PBN is an important relay from the NTS and AP to the forebrain not just for feeding-relevant information, but also in relation to salt appetite and a variety of other regulatory functions. The PBN is also an important site of action for the inhibitory effects of serotonin on feeding behaviour through activation of 5-HT<sub>1B</sub> receptors expressed in the lateral nucleus (Lee and Simansky, 1997) and 5-HT<sub>2C</sub> receptors expressed in the medial nucleus (Trifunovic and Reilly, 2006).

*Hypothalamus.* The hypothalamus was initially identified as a critical site for feeding in the mid 20<sup>th</sup> century through the use of stereotactically placed electrolytic lesions (Anand and Brobeck, 1951; Hetherington and Ranson, 1942), suggesting a medial 'satiety centre' and a more lateral 'hunger centre'. However it was also recognised that lateral lesions potentially compromise fibres of passage, including the median forebrain bundle (Morgane, 1961). Neurotoxic lesions of the mesolimbic dopamine projection, which passes through the lateral edge of the hypothalamus, give rise to profound disturbances of feeding and drinking (Marshall et al., 1974; Ungerstedt, 1971) which can be reversed with low doses of dopamine agonists (Ljungberg and Ungerstedt, 1976). Lateral hypothalamic electrolytic lesions are also associated with somnolence, sensory neglect and akinesia (Levitt and Teitelbaum, 1975). In a similar manner the identification of more medial areas of the hypothalamus as a satiety centre was questioned by the finding that overeating following medial lesions was abolished by presented an adulterated diet (Teitelbaum, 1955) and that the animals were also less willing than controls to work for food on a lean schedule of reinforcement (Teitelbaum, 1957). These early studies vividly demonstrated the importance of detailed behavioural profiling of any experimentally-induced disturbance of feeding and drinking. Nevertheless a considerable body of research since that time has confirmed the importance of specific hypothalamic nuclei in feeding e.g. reviews: (Berthoud, 2002;

Rui, 2013; Yeo and Heisler, 2012). The arcuate (AH), paraventricular (PVH) and lateral (LH) nuclei are of especial significance (Figure 1B).

The AH, adjacent to the third ventricle, is a critical input target for hormones, including pancreatic insulin and amylin, leptin from adipose tissue, and gut peptides such as GLP-1, PYY, CCK, ghrelin and oxyntomodulin. These hormones activate a population of POMC-expressing cells within AH that lead to the release of  $\alpha$ MSH at target neurons elsewhere in the hypothalamus. Activation of these cells is associated with reductions in eating behaviour (Zhan et al., 2013) although this occurs relatively slowly. Activation of a separate population of agouti-related peptide (AGRP) and neuropeptide Y (NPY) expressing cells within AH, that also express receptors for insulin and amylin, leptin, and gut peptides, is associated with more rapid stimulation of eating behaviour (Aponte et al., 2011). AGRP is an endogenous antagonist at melanocortin receptors, including the MC4 receptor, and NPY has a potent orexigenic action when infused into PVH (Stanley et al., 1993).

Activation of a recently identified third population of glutamatergic cells within AH that express oxytocin receptors leads to a rapid decrease in eating behaviour (Fenselau et al., 2017) because of synaptic interactions within the paraventricular nucleus of the hypothalamus (PVH). The arcuate nucleus may also mediate the effects of 5-HT, and drugs such as the 5-HT releaser fenfluramine, on eating via activation of 5-HT<sub>2C</sub> receptors on POMC-containing cells (Cone, 2005; Y Xu et al., 2008). However these hypophagic effects of serotonergic compounds occur rapidly, so presumably there is either a pathway that allows serotonergic stimulation to activate the fast acting glutamatergic AH pathway, or these rapid effects on feeding behaviour are mediated by populations of 5-HT<sub>2C</sub> receptors expressed elsewhere in the CNS.

The PVH is a second hypothalamic area of particular significance to eating behaviour although it has a much broader role in relation to autonomic function (Ferguson et al., 2008). Activation of PVH cells expressing the MC<sub>4</sub>R, receiving their input from POMC-expressing cells in the arcuate nucleus and then projecting to the lateral PBN, generate

physiological satiety (Garfield et al., 2015). A population of oxytocin-expressing cells within PVH are inhibited by AGRP-expressing cells projecting from AH, implying that tonic activity of these cells is responsible for the suppression of eating behaviour (Atasoy et al., 2012). Cells in the mediobasal hypothalamus, which encompasses both AH and PVH, express the growth hormone secretagogue receptor (GHSR) which mediates ghrelin signalling in the brain. A recent series of experiments using a mouse line in which Cre expression is linked to the GHSR promoter in this brain area has demonstrated that this cell population is both necessary and sufficient to generate the feeding response to ghrelin (Mani et al., 2017).

LH was originally identified as a 'feeding centre' by early lesion studies (Anand and Brobeck, 1951), although its potential importance in relation to arousal and sleep had been proposed earlier by Von Economo (Economo, 1930) and then confirmed by later experimental studies in rodents (Levitt and Teitelbaum, 1975). It is now clear that activation of glutamergic cells within the LH, which themselves receive an inhibitory input from the bed nucleus of the stria terminalis (BNST), can inhibit feeding (Jennings et al., 2013). By contrast activation of GABAergic cells that project to the PVH leads to the simulation of feeding (Wu et al., 2015). A population of orexin-expressing cells within the LH is activated by food reward (Harris et al., 2005) and projects widely within the brain, both caudally to structures such as the PBN, to the VTA, and rostrally to ventral pallidum (VP), nucleus accumbens (NAc) and orbitofrontal cortex (Castro et al., 2015). These studies suggest that orexinergic pathways are critical in allowing homeostatic processes that regulate energy balance to influence reward and the conditioned responses that lead to eating behaviour and are consistent with the involvement of the orexin system in addiction-related processes (Harris et al., 2005). However recent data shows that orexin-expressing cells are inactivated during eating and that their activation is associated with voluntary locomotor activity that may be more consistent with an arousal-like function (González et al., 2016; Herrera et al., 2017), so re-evaluation or refinement of this hypothesis may be necessary.

*Reward- and incentive-related structures.* Berridge and colleagues have described the ways in which 'wanting' and 'liking' elicited by food reward are associated with activation of cells in the caudal VP, rostral NAc and related structures (Castro et al., 2015)(Figure 1B). Hedonic responses to sucrose solutions are enhanced by the microinjection of either orexin or opioid agonists in VP (Ho and Berridge, 2013), and by opioid agonists in the NAc (Castro and Berridge, 2014). Cholinergic modulation of feeding behaviour may also involve the NAc (ML Perry et al., 2010). Obese humans chronically treated with the opioid antagonist GSK1521498 show a reduction in the responsiveness of the pallidum, probably including VP, to images of high calorie palatable foods as well as a reduction in a novel measure of motivational responding (Cambridge et al., 2013). Infusion of both GABA-A and GABA-B receptor agonists into the NAc shell leads to a profound activation of feeding behaviour (Stratford and Kelley, 1997), although only GABA-A receptor stimulation leads to enhanced instrumental responding for food (Pulman et al., 2012). One mechanism through which NAc (shell) stimulation of GABA receptors may affect feeding behaviour is by stimulating the population of orexin-expressing cells in the LH (Baldo et al., 2004).

The dopaminergic mesolimbic projection from the VTA to the NAc is importantly involved in response to food reward, and perhaps also in pathological responses to food such as bingeing, although the precise nature of that involvement remains a matter for debate (Salamone and Correa, 2013). More recently it has been shown that cells within the VTA express receptors for a range of other neurotransmitters that mediate such responding. 5-HT<sub>2C</sub> receptors are co-localised with markers for both dopamine and GABA in the VTA (Bubar et al., 2011), and a range of electrophysiological and biochemical data have demonstrated the inhibitory action of 5-HT acting through this receptor subtype (Di Matteo et al., 2001). Activation of VTA 5-HT<sub>2C</sub> receptors reduces feeding and responding for food on a progressive ratio schedule in mice (Valencia-Torres et al., 2016), and reduces sucrose drinking in a binge eating model (P Xu et al., 2017). Other receptors relevant to the modulation of feeding behaviour that are expressed within the VTA, include those for insulin and

leptin (Figlewicz and Benoit, 2009). Activation of insulin receptors in the VTA induces long term depression (LTD) in glutamatergic synapses onto dopaminergic neurons in the VTA, and is also associated with reductions in both feeding behaviour and Pavlovian approach to food-related cues, but has no effect on instrumental responding in a progressive ratio task (Labouèbe et al., 2013). Local administration of leptin into the VTA reduces food intake whereas local knockdown of VTA leptin receptors increases the preference for both sucrose and a high fat diet (Hommel et al., 2006), and the effects of leptin on VTA cell firing resemble those produced by insulin (Thompson and Borgland, 2013).

*Other forebrain structures.* Additional brain areas that are likely to make an important contribution to the modulation of eating behaviour include the hippocampus, amygdala and several prefrontal cortical areas that influence decision making and impulsivity (Figure 1B). Lesions of the hippocampus lead to marked changes in meal patterning (Clifton et al., 1998) that can be interpreted in terms of a deficit in the memory for recent episodes of eating behaviour (Higgs, 2008). In addition hippocampal lesions in the rat impair their ability to retain a discrimination in which the cue is whether they are currently sated or deprived (Davidson et al., 2010). Leptin locally administered into the hippocampus leads to decreased food intake and motivation to feed as well as a reduction in the expression of a food-based conditioned place preference (Kanoski et al., 2011). By contrast hippocampal infusion of ghrelin leads to increased feeding behaviour as well as enhancement of cue-potentiated feeding and a higher breakpoint on a food-rewarded progressive ratio schedule (Kanoski et al., 2013). In these two studies the effects of insulin and ghrelin were selective to ventral rather than dorsal hippocampus. The hippocampus is extensively connected with cortex and reward-related structures through which these effects may be mediated.

An elegant series of studies have suggested that connections between the basolateral nucleus of the amygdala (BLA) and LH also have a critical role in allowing external cues previously associated with food to stimulate feeding behaviour (Petrovich and Gallagher, 2003). This was demonstrated using both first and second order Pavlovian

conditioning procedures. The BLA-LH pathway targets orexigenic cells within the perifornical area of LH (Petrovich et al., 2012), suggesting that the same population of cells may be critical in mediating both the hedonic and reward-related effects discussed earlier, and these cue-related enhancements in feeding behaviour. This body of work is consistent with the much earlier literature on altered feeding responses in the Klüver-Bucy syndrome and single cell recordings in awake non-human primates that are responding to feeding-related stimuli (Rolls, 2006).

There is an extensive literature on the role of prefrontal cortical areas in reward, decision-making and impulsivity (Kim and Lee, 2011). It is likely that this is especially relevant to binge eating disorders and related conditions in which the behavioural phenotype shows some overlap with other conditions associated with impaired impulse control, such as drug addiction (Mole et al., 2015). However, in contrast to studies of (former) drug addicts, functional imaging studies comparing obese individuals, or those with another eating disorder, with control subjects do not show consistent changes in activation of frontal structures to presentation of images of food, cues predicting food, or the actual consumption of food (Ziauddeen et al., 2012), suggesting that care needs to be taken in drawing close parallels between obesity and addictive disorders (Ziauddeen and Fletcher, 2013).

Specific evidence from non-human studies links the ventral medial prefrontal cortex (vmPFC) to amygdalar and hypothalamic feeding circuits. Lesions of vmPFC disrupted cue-potentiated feeding but had no effect on food intake or body weight (Petrovich, Ross, Holland, et al., 2007), and a subsequent study revealed specific activation and recruitment of neurons projecting from BLA to vmPFC during the acquisition of a tone-food pairing that produced cue-induced responding to food (Keefer and Petrovich, 2017). Opioid receptor stimulation in PFC also increases feeding and food-seeking behaviour, but in ways that are distinct from the effect within NAc (Selleck and Baldo, 2017). These authors suggest that the differences arise from the PFC-LH pathway being essentially excitatory in functional terms, whereas the NAc-LH pathway acts to disinhibit its target (Selleck and Baldo, 2017). At a clinical level this suggests that

excessive opioid tone in NAc or PFC may lead to a disorganised, yet high, motivational state that underlies binge eating and related disorders. There is also an extensive literature on the representation of the taste, texture and smell of food within the primate cortex (Rolls, 2006). Neurons in orbitofrontal cortex show responses to food characteristics that are modulated by physiological state. They may also show changes in responding that parallel processes such as sensory-specific satiety. Hence orbitofrontal cortex may be a critical substrate for multimodal representations of food stimuli that are modulated according to their current reward value.

In summary, the last two decades have seen a marked change in the understanding the neural control of feeding behaviour. The homeostatic, reward- and learning-related components of this process rely on an extended neural network including key brainstem nuclei, hypothalamic, limbic and cortical structures, with a complex interplay between them. As is often the case these advances have been permitted by technical developments that allow individual projection sites from cells with an identified neurochemical signature to be either inhibited or excited using a mix of genetic, viral targeting and drug or optogenetic manipulations. These studies have demonstrated a previously unappreciated variety in the relevant neurotransmitters and hormones, and in the range of structures through which they may modulate this distributed network.

## **Targets for the pharmacological treatment of obesity**

This growing understanding of the complexity of the physiological and neural control of feeding behaviour has multiplied the number of potential targets for drug treatment of obesity as described in many recent reviews (Adan, 2013; Chatzigeorgiou et al., 2014; Kennett and Clifton, 2010; Pucci and Finer, 2015; Sargent and Moore, 2009). In addition the output side of energy balance and its relationship to body weight regulation and adiposity is now gaining greater attention. The impact of variation in the gut microbiome is just one example where rapid progress is being made (Thaiss et al., 2016).

### *Monoamine targets*



Drugs enhancing monoamine function were amongst the earliest to be used as anti-obesity treatments, but serotonergic targets seem more likely to be pursued than either noradrenaline or dopamine in the future. There is substantial likelihood of peripheral, especially cardiovascular, side effects with many noradrenergic drugs (Pucci and Finer, 2015) and this has led to compounds such as the mixed monoamine reuptake inhibitor sibutramine being withdrawn from clinical use. However the monoamine releaser phentermine, approved for the treatment of obesity by US regulators in 1959, remains in widespread use. The selective serotonin reuptake inhibitor fenfluramine was also withdrawn due to side effects, including an association with cardiac valvulopathy (Connolly et al., 1997). This spurred studies to identify the 5-HT receptor subtypes that were crucial in modulating feeding behaviour. The 5-HT<sub>2C</sub> receptor was subsequently identified as one through which serotonin (Tecott et al., 1995) and fenfluramine (Vickers et al., 1999) enhance satiation. Subsequently this receptor subtype has received considerable attention in terms of drug development (Voigt and Fink, 2015), leading to clinical trials of the 5-HT<sub>2C</sub> receptor agonist lorcaserin (SR Smith et al., 2009) (Aronne et al., 2014) and its approval by US regulators in 2012. Although there is evidence for a role of other serotonin receptor subtypes in the modulation of feeding, the widespread expression of these receptors elsewhere in the body predicts potential significant side effect issues. To take one example, although activation of the 5-HT<sub>1B</sub> receptor subtype is important in modulating both brainstem (MD Lee et al., 1998) and hypothalamic (Doslikova et al., 2013) control of feeding behaviour, there would be likely concern in relation to potential side effects on pulmonary hypertension with clinical use of selective agonists at this receptor (MacLean and Dempsey, 2009).

### *Peptide targets*

*Gut-related peptides.* Gut-related peptide receptors represent a second obvious set of targets. Amongst these liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist is already approved, in part because it was already in clinical use as an adjunct to the treatment of diabetes when its effects on body weight were recognised. GLP-1, and liraglutide, stimulate the secretion of insulin while inhibiting the secretion of glucagon

from the pancreas, as well as slowing gastric emptying (Drucker and Nauck, 2006). GLP-1 and its analogues also reduce feeding after ICV injection (Turton et al., 1996) and more recent studies have indicated several potential sites of action including, most recently, a possible effect through modulation of raphe serotonergic projections (Anderberg et al., 2017). Following trials in obese subjects without diabetes (Astrup et al., 2009; Pi-Sunyer et al., 2015) the use of liraglutide for treating obesity was approved by European (2015) and US (2014) regulators, and several other GLP-1 receptor agonists are under active investigation (Fosgerau and Hoffmann, 2015; Tan and Bloom, 2013). There is also considerable interest in combining GLP-1 agonism with action at a second peptide receptor. For example, there is a synergistic effect of liraglutide and neurotensin in inhibiting palatable food intake in mice which may indicate clinical potential for this combination (Grunddal et al., 2016).

Polypeptide YY (PYY) and oxyntomodulin analogues provide alternative approaches in this area. PYY reduces food intake in rats (Batterham et al., 2002), although this result is controversial (Tschöp et al 2004) and a detailed behavioural profiling of PYY<sub>3-36</sub> using the behavioural satiety sequence did not support a potential anti-obesity action (Rodgers et al., 2010). PYY is also reported to reduce food intake in normal weight and obese humans (Batterham et al., 2003). Oxyntomodulin reduces food intake in rodents (Dakin et al., 2001) and has the same effect in humans by both increasing energy expenditure and reducing energy intake (Wynne et al., 2006). However PYY- and oxyntomodulin-based therapies have not yet advanced beyond small scale trials.

The potent orexigenic action of NPY would suggest that antagonism of NPY Y1 and Y5 receptors represents a plausible treatment for obesity. Although highly selective Y1 antagonists have been developed and advanced to clinical trials and did lead to additional weight loss in participants on a very low calorie diet, the results were not judged to be clinically meaningful (Erondur et al., 2007). Selective agonism at the MC<sub>4</sub> receptor represents another potential route to obesity treatment that is under active investigation. RM-493 (setmelanotide) is one such a compound that has been shown to shown to reduce food intake in rodents, and to have a synergistic effect with liraglutide

in this regard (Clemmensen et al., 2015). Setmelanotide is currently in Phase 2 trials for obesity and in Prader-Willi syndrome, where excessive food intake and obesity is a common complicating feature.

*Opioid peptides.* There is long standing evidence that opioid peptide receptor antagonists may have substantial effects on diet selection in humans (Yeomans et al., 1990), consistent with their effects on hedonic responding in NAc and VP that were described earlier (Castro and Berridge, 2014; Ho and Berridge, 2013). Such findings have suggested that opioid antagonists might have utility in the treatment of eating disorders, and the  $\mu$  opioid receptor antagonist GSK1521498 has shown promise in obese individuals who also scored highly on a binge-eating clinical screen (Ziauddeen and Fletcher, 2013). An opioid receptor antagonist is one component of Contrave, a fixed dose combination of sustained release naloxone and bupropion, which has been the subject of several Phase 3 trials (Kennett and Clifton, 2010) but no detailed investigations of the effects on detailed components of human feeding behaviour are available. Contrave was approved by US regulators in 2014 and EU regulators in 2015.

*Cannabinoids.* There is also extensive evidence for the involvement of the cannabinoid system in the bidirectional modulation of feeding behaviour and energy balance (DiPatrizio and Piomelli, 2012). The cannabinoid agonists  $\Delta^9$ -tetrahydrocannabinol and anandamide enhance feeding behaviour in a behaviourally selective manner (Williams and Kirkham, 2002). Changes in licking microstructure produced by the cannabinoid antagonist rimonabant suggested a reduced motivation to feed (Thornton-Jones et al., 2007), which is consistent with reduced responding on a second order schedule prior to food reward being made available (Thornton-Jones et al., 2005). Cannabinoid receptors are expressed in both the CNS and peripherally, with the CB1 receptor being more extensively expressed within CNS areas relevant to feeding, including brainstem, several hypothalamic nuclei, and the NAc and VP (Di Marzo and Matias, 2005).

Rimonabant was briefly approved by European regulators for the treatment of obesity, but then withdrawn due to concern over side effects related to depression and suicidal

ideation (Christensen et al., 2007). There was limited evidence of such effects in a small minority of participants within all groups of a trial that used sibtramine, orlistat or a lifestyle modification, raising the possibility that dysphoria may be a more general characteristic of obesity treatment (Faulconbridge et al., 2009). Following the withdrawal of rimonabant several other development programmes for centrally acting cannabinoid antagonists were abandoned, although interest remains in developing peripherally acting compounds that enhance energy expenditure through effects on metabolism or brown adipose tissue (DiPatrizio and Piomelli, 2012).

#### *Other potential targets*

Although the major focus in developing centrally acting anti-obesity drugs has been on relevant neurotransmitter and hormonal systems, there is also interest in cellular signals of energy availability. The highly conserved enzyme 5' adenosine monophosphate-activated protein kinase (AMPK) has attracted considerable attention as an intracellular energy sensor. When the cellular energy status drops AMPK is activated, leading to stimulation of catabolic pathways and ATP production, and a reduction in the activity of anabolic pathways (Long and Zierath, 2006). Within the hypothalamus AMPK plays a critical role in mediating the effects of ghrelin, leptin and insulin. Increased levels of ghrelin stimulate AMPK activity, and pharmacological blockade of this action prevents the expected stimulation of food intake (Stark et al., 2013). AMPK activation permits ghrelin to produce a prolonged activation of AGRP expressing cells in the AH and suggests that it may play a critical role in maintaining motivational states that stabilise behavioural output by acting as a neuronal 'flip-flop' (Yang et al., 2011). This raises the intriguing possibility that hypothalamic AMPK might be a potential target for anti-obesity drug development, although the importance of AMPK in so many other body tissues would make this a challenging goal. There is also evidence that activation of hypothalamic AMPK underlies the appetite- and weight-enhancing effects of second generation antipsychotic drugs such as olanzapine (Zhang et al., 2013).

Serendipity continues to play a role in the identification of potential targets for anti-obesity drugs. The anticonvulsant topiramate is associated with weight loss in clinical use and has subsequently been combined with phentermine in the controlled release preparation Qnexa. Treatment with this drug combination leads to clinically significant weight loss (Allison et al., 2012; Gadde et al., 2011) and it was approved by US regulators in 2012. In rodent models topiramate reduces food intake but may also have independent effects on energetic efficiency and fat deposition (Picard et al., 2000). It may act through enhancement of leptin signalling and also leads to increased expression of anorexigenic neuropeptides including POMC in the hypothalamus (Caricilli et al., 2012).

In summary, an expanded understanding of the neural and physiological substrates has led to a period in which several novel pharmacological treatments for obesity have been introduced with many more at early stage development.

## **Preclinical ‘models’ for eating behaviour**

Preclinical models play an important role in deciding whether development programmes should proceed and can reflect much of the behavioural complexity that is evident in human eating behaviour.

### *Food intake and pair feeding*

The simplest, and perhaps still the most commonly used, preclinical ‘model’ used to screen putative anti-obesity drugs is the measurement of food intake in food-deprived rodents over a period of 30-120 minutes following the treatment of interest. Although this measure has the undeniable advantage of simplicity and ease of use, it also has multiple disadvantages (Vickers and Clifton, 2012). A mammal such as a rodent may eat less for a variety of reasons. The drug treatment may have induced sensory or motor dysfunction, malaise or a hypnotic effect. Even in cases where a drug, such as amphetamine, is rewarding in other contexts, it may nevertheless be able to induce a conditioned taste aversion with repeated administration (Wise et al., 1976). In rarer

cases the interest may be in evaluating potential increases in feeding, for example in evaluating a potential treatment for anorexia. Even in this case there are potential confounds. Mild stress, for example, is a potent stimulant of food intake under chronic conditions, although an acute stressor may lead to a short term decreases or increases in feeding dependent on the specific feeding paradigm that is being used (Adam and Epel, 2007).

However measurements of food intake and body weight remain a useful preliminary, especially when combined with physiological and metabolic measures in a preclinical model of obesity. Genetic models, such as the fatty Zucker rat, which has a missense mutation of the gene for the leptin receptor (Chua et al., 1996), show greatly increased body weight, increased blood lipid levels and insulin resistance as well as hypertension (Kurtz et al., 1989). An alternative approach is to use a varied diet that is high in fat and sugar ('cafeteria' or 'Western' diet) which will reliably induce obesity in rodents. The effects are reversible and recapitulate many of the physiological features of metabolic syndrome (Gomez-Smith et al., 2016). Such diets, may also lead to cognitive impairment in spatial tasks as well as CNS changes characteristic of low grade inflammation (Boitard et al., 2014).

The fundamental question of whether a drug treatment affects the input or output sides of the energy balance equation may be assessed using the pair feeding paradigm. The standard design will normally involve three groups of animals and compares changes in body weight, typically over 7 to 14 days, with food intake being accurately measured each day. Where the focus is on a treatment that is expected to reduce body weight, a control group, treated only with the drug vehicle, will receive ad-libitum food for this period and an experimental group the drug treatment of interest. A third matched control group will also receive vehicle treatment each day but, crucially, will only be allowed the amount of food eaten by the experimental group, which is expected to be less than the first control group. A comparison of the body weights at the end of the experiment will indicate the likely mechanism underlying this difference. If the treatment and matched control groups lose similar amounts of weight then reduced energy intake

is the likely explanation. If, on the other hand, the drug treatment group loses significantly more weight than the food-matched control group then it is likely that enhanced metabolic rate, or increased 'voluntary' activity, has led to the loss of weight. The paradigm has been used, for example, to demonstrate that the melanin-concentrating hormone receptor 1 agonist AZD1979 reduces body weight by decreasing energy intake (Ploj et al., 2016), and that a substantial part of the anti-hyperglycaemic effect of liraglutide is accounted for by a reduction in body weight (Sturis et al., 2003). This technique has also revealed an interesting difference in the effect of various CB1 receptor ligands on energy intake and body weight. Reduced body weight in rats treated with the CB1 receptor inverse agonist rimonabant can be substantially attributed to enhanced energy utilisation (Bajzer et al., 2011), whereas reduced body weight associated with treatment with the neutral CB1 receptor antagonist AM4113 is a consequence of reduced food intake (Cluny et al., 2011).

The design is easily adapted to examine the reasons for increased food intake induced by some antipsychotic drugs that may account for their propensity to induce obesity (Reynolds and Kirk, 2010). In this case both the active treatment and matched control groups receive drug treatment with the matched controls receiving the same amount of food as the other control group. Using this approach it was shown that increased food intake is necessary for olanzapine-induced increases in body weight (Davoodi et al., 2009) in female rats, although it should also be noted that olanzapine treatment enhances adiposity in male rats without increasing body weight (Cooper et al., 2007).

Although pair feeding has been regarded as a gold standard for dissociating the contribution of energy intake and expenditure to body weight changes, there are potential confounds to consider. If the drug treatment does enhance food intake then the food-matched experimental group will become steadily more food-deprived. This, in turn, has been shown to modify their food intake patterns and leads to bingeing immediately after the daily feeding period (Davoodi et al., 2009). A similar effect may be expected in experiments in which a drug-induced reduction in food intake is expected, but instead in the food-matched control group. The substantial alterations in

food intake patterns may in turn affect metabolism, clouding interpretation of the outcome of the experiment (Russell et al., 2008).

#### *Ethologically-based models of feeding behaviour*

Better alternatives to simple intake measures may be chosen by identifying the specific behavioural features of an eating disorder and the likely mechanisms through which a drug treatment might be expected to operate. There has been an emphasis on developing drug treatments that enhance satiation and satiety and several behavioural screens have been developed that have a limited degree of construct, face and predictive validity (Willner, 1984). The most widely used is the behavioural satiety sequence, although meal patterning and licking microstructure paradigms are also valuable.

The behavioural satiety sequence paradigm was derived from observations of Richter and further developed by Antin and others (Antin et al., 1975). The basis of the method is to provide a rodent with a familiar but palatable meal. The behaviour that accompanies and immediately follows feeding is recorded within broad categories such as feed, active, rest and groom. A meal is typically followed by a mix of active behaviour and organised bouts of grooming followed by rest and sleep. Manipulations that are likely to induce malaise or hyperactivity will disturb this natural sequence of behaviour whereas a treatment that enhances satiety would be expected to result in the normal sequence of behaviour occurring after the consumption of a smaller amount of food than would have been expected without that manipulation. A satiety-like effect has been confirmed for a variety of agents including 5-HT<sub>2C</sub> receptor agonists (Hewitt et al., 2002), opioid receptor antagonists (Tallett et al., 2008) and the combination of naltrexone and bupropion (Wright and Rodgers, 2013). Rodgers has provided a recent detailed review of the strengths of this technique (Rodgers, 2016).

Records of meal patterning provide an alternative technique that can provide information about the likely mechanisms underlying a change in food intake patterns. The original methodology was developed by Kissileff who adapted the standard pellet



delivery mechanism used in operant cages to make a single pellet available at all times in the food magazine, and to record when the animal ate (Kissileff, 1970). In this situation rodents eat in clearly defined meals, that is periods in which they take pellets every 10-20 seconds, with much longer intervening periods in which they do not eat (Clifton, 2000). More recently there has been a switch to continuous weighing of a food hopper to provide similar data. This has the advantage of allowing easy modification of the diet, but provides a much less fine grained record that may be susceptible to artefacts caused by animal movement.

A change in the amount of food eaten may be associated with one or more changes in meal parameters. For example, a reduction in meal size, with no change in meal frequency suggests an enhancement of satiation, that is the cues responsible for meal termination, whereas a reduction in meal frequency with no change in meal size would suggest a reduction in hunger, that is the factors responsible for meal initiation. If meal size reduced, but meal frequency increased, with no overall change in food intake then an enhancement of short term satiation factors, but no impact on the sustaining of satiety in the inter-meal interval would account for the data. Reductions in feeding rate during a meal can provide a sensitive indicator of motor impairment, for example dopamine receptor antagonists may both enhance meal size and food intake while simultaneously slowing the rate of feeding (Clifton et al., 1991). Although feeding and drinking behaviour are correlated, drinking should be monitored with similar temporal precision to feeding providing a partial control for effects on feeding behaviour. The value of such data was demonstrated in a study of the effects of a 5-HT<sub>1B</sub> receptor agonist on feeding patterns in which, despite previous reports of a relatively normal but advanced satiety sequence (Halford and Blundell, 1996), the meal patterning approach demonstrated more profound reductions in water intake than in food intake (Lee et al., 2002). In contrast the 5-HT<sub>2C</sub> receptor agonist Ro 60-0175 produced a more profound reduction in food than in water intake (Clifton et al., 2000) which is more consistent with selective enhancement of satiety for food.

A technique with a similar underlying rationale, but operating on a finer time scale, relies on the recording of licking patterns of rats or mice as they ingest a palatable fluid. As with meal patterns, the behaviour is highly structured and distinctly different changes in the bout structure of licking result from changes in fluid palatability or food deprivation (Davis and Perez, 1993). Comparison of the effects of obtained following different drug treatments may therefore give an insight as to how they affect food intake in other contexts. Such studies have suggested that cannabinoid and benzodiazepine agonists increase appetite by enhancing palatability (Higgs and Cooper, 1998; Higgs et al., 2003) and that atypical antipsychotic drugs such as olanzapine reduce satiety signals, leading to excess food intake and weight gain (Hartfield et al., 2003).

#### *Addiction-derived models*

More recently, with the growing appreciation of the importance of reward-related and hedonic influences on eating behaviour (Kenny, 2011), coupled with the identification of extra-hypothalamic forebrain mechanisms through which peripheral signals such as insulin and leptin (Stice et al., 2012), as well as neurotransmitters such as serotonin (Di Matteo et al., 2001), may influence feeding, there has been increasing interest in preclinical behavioural models that may reflect these processes. Such models have frequently been derived from studies of other forms of aberrant reward-related behaviour, especially those involving drugs of abuse (Smith and Robbins, 2013), although the parallels are not exact (Ziauddeen et al., 2012).

Excessive consumption of both food (Schag et al., 2013) and drugs of abuse (Perry and Carroll, 2008) has been linked to increased impulsivity. This provides a clear rationale for the use of tasks that evaluate impulsivity as part of the preclinical screen for drugs that may be used to treat eating disorders. Thus the 5-HT<sub>2C</sub> receptor agonist lorcaserin reduced premature responding in the 5 choice serial reaction time task (5-CSRTT), and also reduced impulsivity in a go-nogo task (Higgins et al., 2016). However, in the same study, lorcaserin was without effect in a delay discounting task.

Eating behaviour may be stimulated by cues associated with the availability of food in rodents (Petrovich, Ross, Gallagher, et al., 2007; Weingarten and Martin, 1989) and young children (Birch et al., 1989) and has a persistent character (Reppucci and Petrovich, 2012). Responding for food in a second order schedule, similar to that used to study the effects of drugs of abuse (Everitt and Robbins, 2000), can be maintained by presentation of a neutral CS associated with the later delivery of food. Responding for such a CS, in the absence of actual food consumption is reduced by 5-HT<sub>2C</sub> receptor agonists indicating an effect other than on satiation and satiety (Somerville et al., 2007). In a related paradigm it has been shown that the 5-HT<sub>2C</sub> receptor agonists lorcaserin and CP-809101 reduce reinstatement of food seeking behaviour after prolonged extinction of VR5-FI20 schedule responding (Higgins et al., 2016). During the reinstatement test the conditioned cue is presented in the absence of food reinforcement. The reinstatement paradigm is also widely used to study drugs of abuse (Crombag et al., 2008).

#### *Binge eating disorder*

Binge eating disorder (BED) was specifically recognised in DSM 5 (American Psychiatric Association, 2013) as an eating disorder subtype in which the bingeing episodes are characterised by “*Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most people would eat in a similar period of time under similar circumstances*” and “*a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)*”. Body weight may be increased but this is not a diagnostic feature. BED has been tentatively linked to disturbances in impulse control or emotion regulation, or to some combination of both factors (Leehr et al., 2015). There are several preclinical models of BED including regular but limited access to sugar, a combination of regular prior food deprivation with stress, and a limited but unpredictable access to palatable food (typically chocolate) that promotes binge eating in the absence of increased body weight (Corwin et al., 2011). The last of these models has been adapted to evaluate putative treatments for BED. The novel  $\mu$  opioid receptor

agonist GSK1521498 reduced binge-like feeding in this paradigm and also decreased the incentive motivation for chocolate provided on a second order schedule (Giuliano et al., 2012). Lis-dexamphetamine has a similar effect which may be mediated through an indirect action at  $\alpha$ 1-adrenoceptors (Vickers et al., 2015). An important issue in using such tasks is the possible confound of eating that is binge-like in character, as opposed to excessive intake that is simply driven by palatability or hedonic factors. Appropriate control groups, not always included in such studies, will help to resolve this issue and are discussed by Corwin (Corwin et al., 2011).

#### *Choosing models of eating behaviour*

This brief survey of preclinical models that may have utility in the development of novel treatments of eating disorders and obesity illustrates several important points. Eating behaviour in rodents and other commonly used experimental animals is subject to much of the same complexity at an individual level that is evident in human eating behaviour. A clearer understanding of the behavioural features associated with obesity and, more broadly, obesity phenotypes, as well as other eating disorders in our own species will almost certainly inform the development of preclinical models that will have a greater degree of face, construct and predictive validity (Willner, 1984) for the drug development process. However the choice of a single model may well be misleading, as will an emphasis that is solely restricted to feeding behaviour. Broader behavioural screens have been described for both rat (Whishaw and Kolb, 2005) and mouse (Crawley, 2000). In addition pre-clinical models developed in non-human animals can aid the development of similar models in humans that may be particularly valuable in the early phases of the drug development process (Murray et al., 2014; Thomas et al., 2014). Thus a comprehensive approach to preclinical behavioural screening of putative drug treatments is likely to enhance the probability of successful identification of putative anti-obesity drugs in the early stages of a drug development programme. The development of 5-HT<sub>2C</sub> receptor agonists for the treatment of obesity provides a good example of this approach in practice. The actions of such compounds were evaluated in a wide variety of preclinical paradigms prior to the successful completion of Phase 1,

2 and 3 clinical trials. Studies published since that time have refined the understanding of the behavioural effects of this class of drug and suggested their utility for the treatment of a broader range of conditions. There is also potential for the results of such studies to be extended to humans, perhaps suggesting ways in which their effectiveness in treating obesity could be enhanced.

## **Concluding remarks**

In this brief review I have provided a synthesis of the literature concerning the neural circuitry underlying feeding and the implications for the identification of targets for anti-obesity drug development, coupled with a description of the preclinical models that are used to evaluate feeding behaviour in the early stages of such programmes. Our understanding of the neural circuitry for feeding has undergone at least two major shifts since the mid 20th century. The three decades following the landmark studies investigating hypothalamic function were dominated by a hypothalamo-centric model of mutually inhibitory centres for appetite and satiety within a homeostatic theoretical perspective. Advances in our understanding of the broader control of both motor and motivated behaviour led to the replacement of this theoretically limited model with one that envisaged the hypothalamus as part of a distributed system that also includes many other structures in the forebrain and brainstem (Hoebel, 1971). In turn this has emphasised that eating behaviour and energy balance are influenced both by homeostatic and non-homeostatic reward-related and cognitive processes. In a sense this simply marks a return to the position adopted in the first decade of the 20th century when Walter Cannon distinguished hunger from appetite on a similar basis (Cannon and Washburn, 1912).

In parallel with these theoretical developments has been the refinement of a wide range of non-human preclinical models which have been used in the basic empirical research that has led to these advances in our understanding of the brain mechanisms that control and modulate feeding behaviour and energy balance. It is less clear whether our understanding of the multifactorial causes of human obesity has advanced

sufficiently to properly guide the choice of preclinical models of eating for a drug development programme. It seems likely that there would be substantial gains from a tighter linking of human clinical and preclinical studies with the non-human preclinical models that are typically used in the earlier stages of drug development.

## REFERENCES

- Adam TC and Epel ES (2007) Stress, eating and the reward system. *Physiology & Behavior* 91(4): 449–458.
- Adan RAH (2013) Mechanisms underlying current and future anti-obesity drugs. *Trends in Neurosciences* 36(2): 133–140.
- Allison DB, Gadde KM, Garvey WT, et al. (2012) Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity* 20(2): 330–342.
- American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*.
- Anand BK and Brobeck JR (1951) Hypothalamic control of food intake in rats and cats. *Yale Journal of Biology and Medicine* 24(2): 123–140.
- Anderberg RH, Richard JE, Eerola K, et al. (2017) Glucagon-Like Peptide 1 and Its Analogs Act in the Dorsal Raphe and Modulate Central Serotonin to Reduce Appetite and Body Weight. *Diabetes* 66(4): 1062–1073.
- Antin J, Gibbs J, Holt J, et al. (1975) Cholecystokinin elicits the complete behavioral sequence of satiety in rats. *Journal of Comparative and Physiological Psychology* 89(7): 784–790.
- Aponte Y, Atasoy D and Sternson SM (2011) AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. *Nature Neuroscience* 14(3): 351–355.
- Aronne L, Shanahan W, Fain R, et al. (2014) Safety and efficacy of lorcaserin: a combined analysis of the BLOOM and BLOSSOM trials. *Postgraduate Medicine* 126(6): 7–18.
- Astrup A, Rössner S, Van Gaal L, et al. (2009) Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 374(9701): 1606–1616.
- Atasoy D, Betley JN, Su HH, et al. (2012) Deconstruction of a neural circuit for hunger. *Nature* 488(7410): 172–177.
- Bajzer M, Olivieri M, Haas MK, et al. (2011) Cannabinoid receptor 1 (CB1) antagonism enhances glucose utilisation and activates brown adipose tissue in diet-induced obese mice. *Diabetologia*, 54(12): 3121–3131.

- Baldo BA, Gual-Bonilla L, Sijapati K, et al. (2004) Activation of a subpopulation of orexin/hypocretin-containing hypothalamic neurons by GABAA receptor-mediated inhibition of the nucleus accumbens shell, but not by exposure to a novel environment. *The European Journal of Neuroscience* 19(2): 376–386.
- Batterham RL, Cohen MA, Ellis SM, et al. (2003) Inhibition of food intake in obese subjects by peptide YY3-36. *The New England Journal of Medicine* 349(10): 941–948.
- Batterham RL, Cowley MA, Small CJ, et al. (2002) Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature* 418(6898): 650–654.
- Benite-Ribeiro SA, Putt DA, Soares-Filho MC, et al. (2016) The link between hypothalamic epigenetic modifications and long-term feeding control. *Appetite* 107: 445–453.
- Berthoud H-R (2002) Multiple neural systems controlling food intake and body weight. *Neuroscience & Biobehavioral Reviews* 26(4): 393–428.
- Berthoud H-R (2012) The neurobiology of food intake in an obesogenic environment. *Proceedings of the Nutrition Society* 71(4): 478–487.
- Birch LL, McPhee L, Sullivan S, et al. (1989) Conditioned meal initiation in young children. *Appetite* 13(2): 105–113.
- Blázquez E, Velázquez E, Hurtado-Carneiro V, et al. (2014) Insulin in the brain: its pathophysiological implications for States related with central insulin resistance, type 2 diabetes and Alzheimer's disease. *Frontiers in Endocrinology*, 5(2): 161.
- Blundell JE, Finlayson G, Gibbons C, et al. (2015) The biology of appetite control: Do resting metabolic rate and fat-free mass drive energy intake? *Physiology & Behavior* 152(Pt B): 473–478.
- Blundell JE, Gibbons C, Caudwell P, et al. (2015) Appetite control and energy balance: impact of exercise. *Obesity Reviews* 16 Suppl 1(18): 67–76.
- Boitard C, Cavaroc A, Sauvant J, et al. (2014) Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is associated with enhanced hippocampal inflammation in rats. *Brain, Behavior, and Immunity* 40: 9–17.
- Bubar MJ, Stutz SJ and Cunningham KA (2011) 5-HT(2C) receptors localize to dopamine and GABA neurons in the rat mesoaccumbens pathway. *PloS One* 6(6): e20508.



- Cambridge VC, Ziauddeen H, Nathan PJ, et al. (2013) Neural and behavioral effects of a novel mu opioid receptor antagonist in binge-eating obese people. *Biological Psychiatry* 73(9): 887–894.
- Cannon WB and Washburn AL (1912) An explanation of hunger. *American Journal of Physiology* 29(5): 441–454.
- Caricilli AM, Penteado E, de Abreu LL, et al. (2012) Topiramate treatment improves hypothalamic insulin and leptin signaling and action and reduces obesity in mice. *Endocrinology* 153(9): 4401–4411.
- Castro DC and Berridge KC (2014) Opioid hedonic hotspot in nucleus accumbens shell: mu, delta, and kappa maps for enhancement of sweetness "liking" and "wanting". *Journal of Neuroscience* 34(12): 4239–4250.
- Castro DC, Cole SL and Berridge KC (2015) Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry. *Frontiers in Systems Neuroscience* 9: 90.
- Chatzigeorgiou A, Kandaraki E, Papavassiliou AG, et al. (2014) Peripheral targets in obesity treatment: a comprehensive update. *Obesity Reviews* 15(6): 487–503.
- Chow CC and Hall KD (2014) Short and long-term energy intake patterns and their implications for human body weight regulation. *Physiology & Behavior* 134: 60–65.
- Christensen R, Kristensen PK, Bartels EM, et al. (2007) Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 370(9600): 1706–1713.
- Chua SC, Chung WK, Wu-Peng XS, et al. (1996) Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. *Science* 271(5251): 994–996.
- Clemmensen C, Finan B, Fischer K, et al. (2015) Dual melanocortin-4 receptor and GLP-1 receptor agonism amplifies metabolic benefits in diet-induced obese mice. *EMBO Molecular Medicine*, 7(3): 288–298.
- Clifton PG (2000) Meal patterning in rodents: psychopharmacological and neuroanatomical studies. *Neuroscience & Biobehavioral Reviews* 24(2): 213–222.
- Clifton PG, Lee MD and Dourish CT (2000) Similarities in the action of Ro 60-0175, a 5-HT<sub>2C</sub> receptor agonist and d-fenfluramine on feeding patterns in the rat. *Psychopharmacologia* 152(3): 256–267.
- Clifton PG, Rusk IN and Cooper SJ (1991) Effects of dopamine D1 and dopamine D2

- antagonists on the free feeding and drinking patterns of rats. *Behavioral Neuroscience* 105(2): 272–281.
- Clifton PG, Vickers SP and Somerville EM (1998) Little and often: ingestive behavior patterns following hippocampal lesions in rats. *Behavioral Neuroscience* 112(3): 502–511.
- Cluny NL, Chambers AP, Vemuri VK, et al. (2011) The neutral cannabinoid CB<sub>1</sub> receptor antagonist AM4113 regulates body weight through changes in energy intake in the rat. *Pharmacology, Biochemistry, and Behavior* 97(3): 537–543.
- Cone RD (2005) Anatomy and regulation of the central melanocortin system. *Nature Neuroscience* 8(5): 571–578.
- Connolly HM, Crary JL, McGoon MD, et al. (1997) Valvular heart disease associated with fenfluramine-phentermine. *The New England Journal of Medicine* 337(9): 581–588.
- Cooper GD, Pickavance LC, Wilding JPH, et al. (2007) Effects of olanzapine in male rats: enhanced adiposity in the absence of hyperphagia, weight gain or metabolic abnormalities. *Journal of psychopharmacology* 21(4): 405–413.
- Corwin RL, Avena NM and Boggiano MM (2011) Feeding and reward: perspectives from three rat models of binge eating. *Physiology & Behavior* 104(1): 87–97.
- Crawley JN (2000) *What's Wrong With My Mouse?: Behavioral Phenotyping of Transgenic and Knockout Mice*. Wiley.
- Crombag HS, Bossert JM, Koya E, et al. (2008) Review. Context-induced relapse to drug seeking: a review. *Philosophical Transactions of the Royal Society B: Biological Sciences* 363(1507): 3233–3243.
- Dakin CL, Gunn I, Small CJ, et al. (2001) Oxyntomodulin inhibits food intake in the rat. *Endocrinology* 142(10): 4244–4250.
- Davidson TL, Kanoski SE, Chan K, et al. (2010) Hippocampal lesions impair retention of discriminative responding based on energy state cues. *Behavioral Neuroscience* 124(1): 97–105.
- Davis JD and Perez MC (1993) Food deprivation- and palatability-induced microstructural changes in ingestive behavior. *The American journal of physiology* 264(1 Pt 2): R97–103.
- Davoodi N, Kalinichev M, Korneev SA, et al. (2009) Hyperphagia and increased meal

size are responsible for weight gain in rats treated sub-chronically with olanzapine. *Psychopharmacology* 203(4): 693–702.

Di Marzo V and Matias I (2005) Endocannabinoid control of food intake and energy balance. *Nature Neuroscience* 8(5): 585–589.

Di Matteo V, De Blasi A, Di Giulio C, et al. (2001) Role of 5-HT(2C) receptors in the control of central dopamine function. *Trends in Pharmacological Sciences* 22(5): 229–232.

DiPatrizio NV and Piomelli D (2012) The thrifty lipids: endocannabinoids and the neural control of energy conservation. *Trends in Neurosciences* 35(7): 403–411.

Doslikova B, Garfield AS, Shaw J, et al. (2013) 5-HT<sub>2C</sub> receptor agonist anorectic efficacy potentiated by 5-HT<sub>1B</sub> receptor agonist coapplication: an effect mediated via increased proportion of pro-opiomelanocortin neurons activated. *Journal of Neuroscience* 33(23): 9800–9804.

Drucker DJ and Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 368(9548): 1696–1705.

Economo CV (1930) Sleep as a Problem of Localization. *The Journal of Nervous and Mental Disease* 71(3): 249–259.

Erondur N, Wadden T, Gantz I, et al. (2007) Effect of NPY<sub>5R</sub> antagonist MK-0557 on weight regain after very-low-calorie diet-induced weight loss. *Obesity* 15(4): 895–905.

Everitt BJ and Robbins TW (2000) Second-order schedules of drug reinforcement in rats and monkeys: measurement of reinforcing efficacy and drug-seeking behaviour. *Psychopharmacology* 153(1): 17–30.

Fan W, Ellacott KLJ, Halatchev IG, et al. (2004) Cholecystokinin-mediated suppression of feeding involves the brainstem melanocortin system. *Nature Neuroscience* 7(4): 335–336.

Faulconbridge LF, Wadden TA, Berkowitz RI, et al. (2009) Changes in symptoms of depression with weight loss: results of a randomized trial. *Obesity* 17(5): 1009–1016.

Fenselau H, Campbell JN, Verstegen AMJ, et al. (2017) A rapidly acting glutamatergic ARC→PVH satiety circuit postsynaptically regulated by  $\alpha$ -MSH. *Nature Neuroscience* 20(1): 42–51.

- Ferguson AV, Latchford KJ and Samson WK (2008) The paraventricular nucleus of the hypothalamus - a potential target for integrative treatment of autonomic dysfunction. *Expert Opinion on Therapeutic Targets* 12(6): 717–727.
- Figlewicz DP and Benoit SC (2009) Insulin, leptin, and food reward: update 2008. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* 296(1): R9–R19.
- Fosgerau K and Hoffmann T (2015) Peptide therapeutics: current status and future directions. *Drug Discovery Today* 20(1): 122–128.
- Gadde KM, Allison DB, Ryan DH, et al. (2011) Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 377(9774): 1341–1352.
- Garfield AS, Li C, Madara JC, et al. (2015) A neural basis for melanocortin-4 receptor-regulated appetite. *Nature Neuroscience* 18(6): 863–871.
- Gelegen C, Chandarana K, Choudhury AI, et al. (2012) Regulation of hindbrain Pyy expression by acute food deprivation, prolonged caloric restriction, and weight loss surgery in mice. *American Journal of Physiology. Endocrinology and Metabolism* 303(5): E659–68.
- Giuliano C, Robbins TW, Nathan PJ, et al. (2012) Inhibition of Opioid Transmission at the  $[\mu]$ -Opioid Receptor Prevents Both Food Seeking and Binge-Like Eating. *Neuropsychopharmacology* 37(12): 2643–2652.
- Gomez-Smith M, Karthikeyan S, Jeffers MS, et al. (2016) A physiological characterization of the Cafeteria diet model of metabolic syndrome in the rat. *Physiology & Behavior* 167: 382–391.
- González JA, Jensen LT, Iordanidou P, et al. (2016) Inhibitory Interplay between Orexin Neurons and Eating. *Current Biology : CB* 26(18): 2486–2491.
- Göke R, Larsen PJ, Mikkelsen JD, et al. (1995) Distribution of GLP-1 binding sites in the rat brain: evidence that exendin-4 is a ligand of brain GLP-1 binding sites. *The European Journal of Neuroscience* 7(11): 2294–2300.
- Gribble FM and Reimann F (2016) Enteroendocrine Cells: Chemosensors in the Intestinal Epithelium. *Annual Review of Physiology* 78: 277–299.
- Grill HJ and Hayes MR (2012) Hindbrain neurons as an essential hub in the neuroanatomically distributed control of energy balance. *Cell Metabolism* 16(3): 382–391.

296–309.

- Grunddal KV, Ratner CF, Svendsen B, et al. (2016) Neurotensin Is Coexpressed, Coreleased, and Acts Together With GLP-1 and PYY in Enteroendocrine Control of Metabolism. *Endocrinology* 157(1): 176–194.
- Halford JC and Blundell JE (1996) The 5-HT<sub>1B</sub> receptor agonist CP-94,253 reduces food intake and preserves the behavioural satiety sequence. *Physiology & Behavior* 60(3): 933–939.
- Halford JC, Wanninayake SC and Blundell JE (1998) Behavioral satiety sequence (BSS) for the diagnosis of drug action on food intake. *Pharmacology, Biochemistry, and Behavior* 61(2): 159–168.
- Hall KD (2010) Predicting metabolic adaptation, body weight change, and energy intake in humans. *American Journal of Physiology. Endocrinology and Metabolism* 298(3): E449–66.
- Harris GC, Wimmer M and Aston-Jones G (2005) A role for lateral hypothalamic orexin neurons in reward seeking. *Nature* 437(7058): 556–559.
- Hartfield AW, Moore NA and Clifton PG (2003) Effects of clozapine, olanzapine and haloperidol on the microstructure of ingestive behaviour in the rat. *Psychopharmacologia* 167(2): 115–122.
- Herrera CG, Ponomarenko A, Korotkova T, et al. (2017) Sleep & metabolism: The multitasking ability of lateral hypothalamic inhibitory circuitries. *Frontiers in Neuroendocrinology* 44: 27–34.
- Hetherington AW and Ranson SW (1942) The spontaneous activity and food intake of rats with hypothalamic lesions. *American Journal of Physiology*. 136(4): 609–617.
- Hewitt KN, Lee MD, Dourish CT, et al. (2002) Serotonin 2C receptor agonists and the behavioural satiety sequence in mice. *Pharmacology, Biochemistry, and Behavior* 71(4): 691–700.
- Higgins GA, Silenieks LB, Altherr EB, et al. (2016) Lorcaserin and CP-809101 reduce motor impulsivity and reinstatement of food seeking behavior in male rats: Implications for understanding the anti-obesity property of 5-HT<sub>2C</sub> receptor agonists. *Psychopharmacology* 233(14): 2841–2856.
- Higgs S (2008) Cognitive influences on food intake: the effects of manipulating memory for recent eating. *Physiology & Behavior* 94(5): 734–739.

- Higgs S and Cooper SJ (1998) Effects of benzodiazepine receptor ligands on the ingestion of sucrose, intralipid, and maltodextrin: an investigation using a microstructural analysis of licking behavior in a brief contact test. *Behavioral Neuroscience* 112(2): 447–457.
- Higgs S, Williams CM and Kirkham TC (2003) Cannabinoid influences on palatability: microstructural analysis of sucrose drinking after delta(9)-tetrahydrocannabinol, anandamide, 2-arachidonoyl glycerol and SR141716. *Psychopharmacologia* 165(4): 370–377.
- Ho C-Y and Berridge KC (2013) An orexin hotspot in ventral pallidum amplifies hedonic ‘liking’ for sweetness. *Neuropsychopharmacology* 38(9): 1655–1664.
- Hoebel BG (1971) Feeding: neural control of intake. *Annual Review of Physiology* 33(1): 533–568.
- Hommel JD, Trinko R, Sears RM, et al. (2006) Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron* 51(6): 801–810.
- Jennings JH, Rizzi G, Stamatakis AM, et al. (2013) The inhibitory circuit architecture of the lateral hypothalamus orchestrates feeding. *Science* 341(6153): 1517–1521.
- Jordan SD, Könner AC and Brüning JC (2010) Sensing the fuels: glucose and lipid signaling in the CNS controlling energy homeostasis. *Cellular and Molecular Life Sciences* 67(19): 3255–3273.
- Kanoski SE, Fortin SM, Ricks KM, et al. (2013) Ghrelin signaling in the ventral hippocampus stimulates learned and motivational aspects of feeding via PI3K-Akt signaling. *Biological Psychiatry* 73(9): 915–923.
- Kanoski SE, Hayes MR, Greenwald HS, et al. (2011) Hippocampal leptin signaling reduces food intake and modulates food-related memory processing. *Neuropsychopharmacology* 36(9): 1859–1870.
- Kanoski SE, Zhao S, Guarnieri DJ, et al. (2012) Endogenous leptin receptor signaling in the medial nucleus tractus solitarius affects meal size and potentiates intestinal satiation signals. *American Journal of Physiology. Endocrinology and Metabolism* 303(4): E496–503.
- Karra E, Chandarana K and Batterham RL (2009) The role of peptide YY in appetite regulation and obesity. *The Journal of Physiology* 587(Pt 1): 19–25.
- Keefer SE and Petrovich GD (2017) Distinct recruitment of basolateral amygdala-medial prefrontal cortex pathways across Pavlovian appetitive conditioning.

*Neurobiology of Learning and Memory* 141: 27–32.

Kelley AE, Baldo BA and Pratt WE (2005) A proposed hypothalamic-thalamic-striatal axis for the integration of energy balance, arousal, and food reward. *The Journal of Comparative Neurology* 493(1): 72–85.

Kennett GA and Clifton PG (2010) New approaches to the pharmacological treatment of obesity: can they break through the efficacy barrier? *Pharmacology, Biochemistry, and Behavior* 97(1): 63–83.

Kenny PJ (2011) Reward mechanisms in obesity: new insights and future directions. *Neuron* 69(4): 664–679.

Kim S and Lee D (2011) Prefrontal cortex and impulsive decision making. *Biological Psychiatry* 69(12): 1140–1146.

Kissileff HR (1970) Free feeding in normal and 'recovered lateral' rats monitored by a pellet-detecting eatometer. *Physiology & Behavior* 5(2): 163–173.

Kurtz TW, Morris RC and Pershadsingh HA (1989) The Zucker fatty rat as a genetic model of obesity and hypertension. *Hypertension* 13(6 Pt 2): 896–901.

Labouèbe G, Liu S, Dias C, et al. (2013) Insulin induces long-term depression of ventral tegmental area dopamine neurons via endocannabinoids. *Nature Neuroscience* 16(3): 300–308.

Larsen PJ, Tang-Christensen M, Holst JJ, et al. (1997) Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. *Neuroscience* 77(1): 257–270.

Lee MD and Simansky KJ (1997) CP-94, 253: a selective serotonin<sub>1B</sub> (5-HT<sub>1B</sub>) agonist that promotes satiety. *Psychopharmacologia* 131(3): 264–270.

Lee MD, Aloyo VJ, Fluharty SJ, et al. (1998) Infusion of the serotonin<sub>1B</sub> (5-HT<sub>1B</sub>) agonist CP-93,129 into the parabrachial nucleus potently and selectively reduces food intake in rats. *Psychopharmacologia* 136(3): 304–307.

Lee MD, Kennett GA, Dourish CT, et al. (2002) 5-HT<sub>1B</sub> receptors modulate components of satiety in the rat: behavioural and pharmacological analyses of the selective serotonin<sub>1B</sub> agonist CP-94,253. *Psychopharmacologia* 164(1): 49–60.

Leehr EJ, Krohmer K, Schag K, et al. (2015) Emotion regulation model in binge eating disorder and obesity--a systematic review. *Neuroscience & Biobehavioral Reviews* 49: 125–134.

- Levitt DR and Teitelbaum P (1975) Somnolence, akinesia, and sensory activation of motivated behavior in the lateral hypothalamic syndrome. *Proceedings of the National Academy of Sciences of the United States of America* 72(7): 2819–2823.
- Ljungberg T and Ungerstedt U (1976) Reinstatement of eating by dopamine agonists in aphagic dopamine denervated rats. *Physiology & Behavior* 16(3): 277–283.
- Long YC and Zierath JR (2006) AMP-activated protein kinase signaling in metabolic regulation. *Journal of Clinical Investigation* 116(7): 1776–1783.
- Lutz TA (2013) The interaction of amylin with other hormones in the control of eating. *Diabetes, Obesity & Metabolism* 15(2): 99–111.
- MacLean MR and Dempsey Y (2009) Serotonin and pulmonary hypertension--from bench to bedside? *Current Opinion in Pharmacology* 9(3): 281–286.
- Mani BK, Osborne-Lawrence S, Mequinion M, et al. (2017) The role of ghrelin-responsive mediobasal hypothalamic neurons in mediating feeding responses to fasting. *Molecular Metabolism* 6(8): 882–896.
- Marshall JF, Richardson JS and Teitelbaum P (1974) Nigrostriatal bundle damage and the lateral hypothalamic syndrome. *Journal of comparative and physiological psychology* 87(5): 808–830.
- Miceli MO, Post CA and der Kooy van D (1987) Catecholamine and serotonin colocalization in projection neurons of the area postrema. *Brain Research* 412(2): 381–385.
- Mole TB, Irvine MA, Worbe Y, et al. (2015) Impulsivity in disorders of food and drug misuse. *Psychological Medicine* 45(4): 771–782.
- Mollet A, Gilg S, Riediger T, et al. (2004) Infusion of the amylin antagonist AC 187 into the area postrema increases food intake in rats. *Physiology & Behavior* 81(1): 149–155.
- Moran TH and Kinzig KP (2004) Gastrointestinal satiety signals II. Cholecystokinin. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 286(2): G183–8.
- Morgane PJ (1961) Medial forebrain bundle and 'feeding centers' of the hypothalamus. *The Journal of Comparative Neurology* 117: 1–25.
- Murray E, Brouwer S, McCutcheon R, et al. (2014) Opposing neural effects of naltrexone on food reward and aversion: implications for the treatment of obesity.



*Psychopharmacology* 231(22): 4323–4335.

Oertel W and Schulz JB (2016) Current and experimental treatments of Parkinson disease: A guide for neuroscientists. *Journal of Neurochemistry* 139 Suppl 1(Suppl 3): 325–337.

Pangalos MN, Schechter LE and Hurko O (2007) Drug development for CNS disorders: strategies for balancing risk and reducing attrition. *Nature Reviews Drug discovery* 6(7): 521–532.

Parise EM, Lilly N, Kay K, et al. (2011) Evidence for the role of hindbrain orexin-1 receptors in the control of meal size. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* 301(6): R1692–R1699.

Perelló M, Scott MM, Sakata I, et al. (2012) Functional implications of limited leptin receptor and ghrelin receptor coexpression in the brain. *The Journal of Comparative Neurology* 520(2): 281–294.

Perry JL and Carroll ME (2008) The role of impulsive behavior in drug abuse. 4 ed. *Psychopharmacologia* 200(1): 1–26.

Perry ML, Andrzejewski ME, Bushek SM, et al. (2010) Intra-accumbens infusion of a muscarinic antagonist reduces food intake without altering the incentive properties of food-associated cues. *Behavioral Neuroscience* 124(1): 44–54.

Petrovich GD and Gallagher M (2003) Amygdala subsystems and control of feeding behavior by learned cues. *Annals of the New York Academy of Sciences* 985: 251–262.

Petrovich GD, Hobin MP and Reppucci CJ (2012) Selective Fos induction in hypothalamic orexin/hypocretin, but not melanin-concentrating hormone neurons, by a learned food-cue that stimulates feeding in sated rats. *Neuroscience* 224: 70–80.

Petrovich GD, Ross CA, Gallagher M, et al. (2007) Learned contextual cue potentiates eating in rats. *Physiology & Behavior* 90(2-3): 362–367.

Petrovich GD, Ross CA, Holland PC, et al. (2007) Medial prefrontal cortex is necessary for an appetitive contextual conditioned stimulus to promote eating in sated rats. *Journal of Neuroscience* 27(24): 6436–6441.

Pi-Sunyer X, Astrup A, Fujioka K, et al. (2015) A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *The New England Journal of Medicine* 373(1): 11–22.

- Picard F, Deshaies Y, Lalonde J, et al. (2000) Topiramate reduces energy and fat gains in lean (Fa/?) and obese (fa/fa) Zucker rats. *Obesity Research* 8(9): 656–663.
- Ploj K, Benthem L, Kakol-Palm D, et al. (2016) Effects of a novel potent melanin-concentrating hormone receptor 1 antagonist, AZD1979, on body weight homeostasis in mice and dogs. *British Journal of Pharmacology* 173(18): 2739–2751.
- Prentice AM and Jebb SA (1995) Obesity in Britain: gluttony or sloth? *British Medical Journal* 311(7002): 437–439.
- Prentice AM and Jebb SA (2003) Fast foods, energy density and obesity: a possible mechanistic link. *Obesity Reviews* 4(4): 187–194.
- Pucci A and Finer N (2015) New medications for treatment of obesity: metabolic and cardiovascular effects. *The Canadian Journal of Cardiology* 31(2): 142–152.
- Pulman KGT, Somerville EM and Clifton PG (2012) Intra-accumbens baclofen, but not muscimol, increases second order instrumental responding for food reward in rats. *PloS One* 7(7): e40057.
- Reppucci CJ and Petrovich GD (2012) Learned food-cue stimulates persistent feeding in sated rats. *Appetite* 59(2): 437–447.
- Reynolds GP and Kirk SL (2010) Metabolic side effects of antipsychotic drug treatment--pharmacological mechanisms. *Pharmacology & Therapeutics* 125(1): 169–179.
- Ridaura VK, Faith JJ, Rey FE, et al. (2013) Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 341(6150): 1241214.
- Rodgers RJ (2016) Bench to bedside in appetite research: Lost in translation? *Neuroscience & Biobehavioral Reviews*.
- Rodgers RJ, Holch P and Tallett AJ (2010) Behavioural satiety sequence (BSS): separating wheat from chaff in the behavioural pharmacology of appetite. *Pharmacology, Biochemistry, and Behavior* 97(1): 3–14.
- Rolls ET (2006) Brain mechanisms underlying flavour and appetite. *Philosophical transactions of the Royal Society of London Series B, Biological Sciences* 361(1471): 1123–1136.
- Roman CW, Sloat SR and Palmiter RD (2017) A tale of two circuits: CCK(NTS) neuron

stimulation controls appetite and induces opposing motivational states by projections to distinct brain regions. *Neuroscience* 358: 316–324.

Rui L (2013) Brain regulation of energy balance and body weight. *Reviews in Endocrine & Metabolic Disorders* 14(4): 387–407.

Russell JC, Proctor SD, Kelly SE, et al. (2008) Pair feeding-mediated changes in metabolism: stress response and pathophysiology in insulin-resistant, atherosclerosis-prone JCR:LA-cp rats. *American Journal of Physiology. Endocrinology and Metabolism* 294(6): E1078–87.

Salamone JD and Correa M (2013) Dopamine and food addiction: lexicon badly needed. *Biological Psychiatry* 73(9): e15–24.

Sargent BJ and Moore NA (2009) New central targets for the treatment of obesity. *British Journal of Clinical Pharmacology* 68(6): 852–860.

Scannell JW and Bosley J (2016) When Quality Beats Quantity: Decision Theory, Drug Discovery, and the Reproducibility Crisis. Gasparini M (ed.), *PloS one* 11(2): e0147215.

Schag K, Schönleber J, Teufel M, et al. (2013) Food-related impulsivity in obesity and binge eating disorder--a systematic review. *Obesity Reviews* 14(6): 477–495.

Selleck RA and Baldo BA (2017) Feeding-modulatory effects of mu-opioids in the medial prefrontal cortex: a review of recent findings and comparison to opioid actions in the nucleus accumbens. *Psychopharmacology* 92: 545.

Smietana K, Siatkowski M and Møller M (2016) Trends in clinical success rates. *Nature Reviews Drug Discovery* 15(6): 379–380.

Smith DG and Robbins TW (2013) The neurobiological underpinnings of obesity and binge eating: a rationale for adopting the food addiction model. *Biological Psychiatry* 73(9): 804–810.

Smith SR, Prosser WA, Donahue DJ, et al. (2009) Lorcaserin (APD356), a selective 5-HT(2C) agonist, reduces body weight in obese men and women. *Obesity* 17(3): 494–503.

Somerville EM, Horwood JM, Lee MD, et al. (2007) 5-HT(2C) receptor activation inhibits appetitive and consummatory components of feeding and increases brain c-fos immunoreactivity in mice. *The European Journal of Neuroscience* 25(10): 3115–3124.

- Stanley BG, Magdalin W, Seirafi A, et al. (1993) The perifornical area: the major focus of (a) patchily distributed hypothalamic neuropeptide Y-sensitive feeding system(s). *Brain Research* 604(1-2): 304–317.
- Stark R, Ashley SE and Andrews ZB (2013) AMPK and the neuroendocrine regulation of appetite and energy expenditure. *Molecular and Cellular Endocrinology* 366(2): 215–223.
- Stice E, Figlewicz DP, Gosnell BA, et al. (2012) The contribution of brain reward circuits to the obesity epidemic. *Neuroscience & Biobehavioral Reviews*.
- Stratford TR and Kelley AE (1997) GABA in the nucleus accumbens shell participates in the central regulation of feeding behavior. *Journal of Neuroscience* 17(11): 4434–4440.
- Sturis J, Gotfredsen CF, Rømer J, et al. (2003) GLP-1 derivative liraglutide in rats with beta-cell deficiencies: influence of metabolic state on beta-cell mass dynamics. *British Journal of Pharmacology* 140(1): 123–132.
- Tallett AJ, Blundell JE and Rodgers RJ (2008) Behaviourally-selective hypophagic effects of naloxone in non-deprived male rats presented with palatable food. *Behavioural Brain Research* 187(2): 417–427.
- Tan T and Bloom S (2013) Gut hormones as therapeutic agents in treatment of diabetes and obesity. *Current Opinion in Pharmacology* 13(6): 996–1001.
- Tecott LH, Sun LM, Akana SF, et al. (1995) Eating disorder and epilepsy in mice lacking 5-HT<sub>2C</sub> serotonin receptors. *Nature* 374(6522): 542–546.
- Teitelbaum P (1955) Sensory control of hypothalamic hyperphagia. *Journal of Comparative and Physiological Psychology* 48(3): 156–163.
- Teitelbaum P (1957) Random and food-directed activity in hyperphagic and normal rats. *Journal of Comparative and Physiological Psychology* 50(5): 486–490.
- Thaiss CA, Itav S, Rothschild D, et al. (2016) Persistent microbiome alterations modulate the rate of post-dieting weight regain. *Nature* 540(7634): 544–551.
- Thomas JM, Dourish CT, Tomlinson JW, et al. (2014) Effects of the 5-HT<sub>2C</sub> receptor agonist meta-chlorophenylpiperazine on appetite, food intake and emotional processing in healthy volunteers. *Psychopharmacology* 231(12): 2449–2459.
- Thompson JL and Borgland SL (2013) Presynaptic leptin action suppresses excitatory synaptic transmission onto ventral tegmental area dopamine neurons. *Biological*

*Psychiatry* 73(9): 860–868.

Thornton-Jones ZD, Kennett GA, Vickers SP, et al. (2007) A comparison of the effects of the CB(1) receptor antagonist SR141716A, pre-feeding and changed palatability on the microstructure of ingestive behaviour. *Psychopharmacologia* 193(1): 1–9.

Thornton-Jones ZD, Vickers SP and Clifton PG (2005) The cannabinoid CB1 receptor antagonist SR141716A reduces appetitive and consummatory responses for food. *Psychopharmacologia* 179(2): 452–460.

Trifunovic R and Reilly S (2006) Medial parabrachial nucleus neurons modulate d-fenfluramine-induced anorexia through 5HT<sub>2C</sub> receptors. *Brain Research* 1067(1): 170–176.

Tschöp, M et al. (2004). Physiology: does gut hormone PYY<sub>3-36</sub> decrease food intake in rodents? *Nature*, 430(6996): 1-2.

Turton MD, O'Shea D, Gunn I, et al. (1996) A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 379(6560): 69–72.

Ungerstedt U (1971) Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta physiologica Scandinavica. Supplementum* 367: 95–122.

Valencia-Torres L, Olarte-Sánchez CM, Lyons DJ, et al. (2016) Activation of Ventral Tegmental Area 5-HT<sub>2C</sub> Receptors Reduces Incentive Motivation. *Neuropsychopharmacology* 42: 1511-1521.

Vickers SP and Clifton PG (2012) Animal models to explore the effects of CNS drugs on food intake and energy expenditure. *Neuropharmacology* 63(1): 124–131.

Vickers SP, Clifton PG, Dourish CT, et al. (1999) Reduced satiating effect of d-fenfluramine in serotonin 5-HT<sub>2C</sub> receptor mutant mice. *Psychopharmacologia* 143(3): 309–314.

Vickers SP, Hackett D, Murray F, et al. (2015) Effects of lisdexamfetamine in a rat model of binge-eating. *Journal of psychopharmacology* 29(12): 1290–1307.

Voigt J-P and Fink H (2015) Serotonin controlling feeding and satiety. *Behavioural Brain Research* 277: 14–31.

Weingarten HP and Martin GM (1989) Mechanisms of conditioned meal initiation. *Physiology & Behavior* 45(4): 735–740.

- Whishaw IQ and Kolb B (2005) The behavior of the laboratory rat. *A Handbook with Tests*.
- Whiting L, McCutcheon JE, Boyle CN, et al. (2017) The area postrema (AP) and the parabrachial nucleus (PBN) are important sites for salmon calcitonin (sCT) to decrease evoked phasic dopamine release in the nucleus accumbens (NAc). *Physiology & Behavior* 176: 9–16.
- Williams CM and Kirkham TC (2002) Observational analysis of feeding induced by Delta9-THC and anandamide. *Physiology & Behavior* 76(2): 241–250.
- Williams DL (2014) Neural integration of satiation and food reward: role of GLP-1 and orexin pathways. *Physiology & Behavior* 136: 194–199.
- Willner P (1984) The validity of animal models of depression. *Psychopharmacologia* 83(1): 1–16.
- Wise RA, Yokel RA and DeWit H (1976) Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. *Science* 191(4233): 1273–1275.
- Wright FL and Rodgers RJ (2013) Acute behavioural effects of bupropion and naltrexone, alone and in combination, in non-deprived male rats presented with palatable mash. *Psychopharmacology* 228(2): 291–307.
- Wu Z, Kim ER, Sun H, et al. (2015) GABAergic projections from lateral hypothalamus to paraventricular hypothalamic nucleus promote feeding. *Journal of Neuroscience, Society for Neuroscience* 35(8): 3312–3318.
- Wynne K, Park AJ, Small CJ, et al. (2006) Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial. *International Journal of Obesity and Related Metabolic Disorders* 30(12): 1729–1736.
- Xu P, He Y, Cao X, et al. (2017) Activation of Serotonin 2C Receptors in Dopamine Neurons Inhibits Binge-like Eating in Mice. *Biological Psychiatry* 81(9): 737–747.
- Xu Y, Jones JE, Kohno D, et al. (2008) 5-HT<sub>2</sub>CRs expressed by pro-opiomelanocortin neurons regulate energy homeostasis. *Neuron* 60(4): 582–589.
- Yang Y, Atasoy D, Su HH, et al. (2011) Hunger states switch a flip-flop memory circuit via a synaptic AMPK-dependent positive feedback loop. *Cell* 146(6): 992–1003.
- Yeo GSH and Heisler LK (2012) Unraveling the brain regulation of appetite: lessons

- from genetics. *Nature Neuroscience* 15(10): 1343–1349.
- Yeomans MR, Wright P, Macleod HA, et al. (1990) Effects of nalmefene on feeding in humans. Dissociation of hunger and palatability. *Psychopharmacologia* 100(3): 426–432.
- Zhan C, Zhou J, Feng Q, et al. (2013) Acute and long-term suppression of feeding behavior by POMC neurons in the brainstem and hypothalamus, respectively. *Journal of Neuroscience* 33(8): 3624–3632.
- Zhang Q, Deng C and Huang X-F (2013) The role of ghrelin signalling in second-generation antipsychotic-induced weight gain. *Psychoneuroendocrinology* 38(11): 2423–2438.
- Ziauddeen H and Fletcher PC (2013) Is food addiction a valid and useful concept? *Obesity Reviews* 14(1): 19–28.
- Ziauddeen H, Farooqi IS and Fletcher PC (2012) Obesity and the brain: how convincing is the addiction model? *Nature Reviews Neuroscience* 13(4): 279–286.

## Figure Legend

Figure 1. Diagrammatic representation of the major pathways referred to in the text that project from brainstem nuclei (A) or from the forebrain (B). Projections terminating with a dot have a broadly inhibitory functional effect on feeding behaviour, whereas those terminating with an arrow have a broadly facilitatory effect. Relevant brain areas are shown in violet except for the NAc where the graded colours represent the gradient of response described by Berridge and co-workers (see text) with green and purple respectively used to code appetitive and aversive responses. Neurochemically defined pathways are colour coded and the remainder shown in black. The brain outline is based on that for the mouse.



Figure 1

